Remarks

Claims 1, 4-23, 25-32, 67, 70, 92, 93, and 95-105 were examined in this case. All claims were rejected in the Final Office Action. The present Submission amends claims 1, 8, 9, 12, 14, 25 – 27, 92, 93, and 105, cancels claims 4-7, 10-11, 13, 23, 29 – 32, 67, 70, 75-91, 96, and 98 - 102, and adds claims 106 and 107. Each of the objections and rejections levied in the Final Office Action, and also the issues raised in the Advisory Action, is addressed individually below.

Support for the Amendments

Support for new claims 106 and 107 can be found in the specification at page 32, lines 20-22. Support for the amendment to claims 8, 9, and 92 can be found in the specification at page 26, line 19 to page 27, line 10 and Figures 22 and 23, which states,

> Competition analysis (Figure 22) has been employed to define antibodies with similar binding sites in HCV E2. Seven HMAbs were biotinylated and the binding of the biotinylated antibodies to HCV E2 in the presence of increasing amounts of competing HCV HMAbs was determined. Antibodies that cross-competed significantly were grouped together. Regions of HCV E2 that contained the binding sites were localized using a series of HCV E2 deletion constructs (Figure 23). Four competition groups were defined. Group I consisted of five HMAbs, CBH-2, -8E, -5, -8C, and -11. Antibodies from this group inhibit binding of HCV E2 to CD81 and recognize conserved epitopes localized to HCV E2 amino acids 411 to 644. Group II consists of HMAbs CBH-7 and XTL-U68, which recognize a highly conserved epitope located between HCV E2 amino acids 470-644. Antibodies from groups I and II exhibited minimal cross-competition. Group III consisted of three antibodies, CBH-4G, -4B, and -4D, that do not inhibit binding of HCV E2 to CD81 and recognize epitopes between HCV E2 amino acids 470 to 644.

New Objection

The Examiner states that the Amendment filed February 10, 2003 is objected to under 35 U.S.C 132 because it introduces new matter into the disclosure. The added material which the Examiner asserts is not supported by the original disclosure is as follows: "The dissociation constants for these antibodies for their epitopes rages from less than 10^{-7} to less than 10^{-8} to less than 10^{-9}M" (page 6, line 14). In response, the material added at page 6, line 14, in the second sentence has been amended to change the K_D ranges to K_D values as recited in original claims 4-7. Support for this amendment can be found in claims 4-7 in the application as filed. Withdrawal of this objection is requested.

Rejections Under 35 U.S.C § 112, Second Paragraph

Claims 32, 67, 70, and 98-100 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for a variety of reasons. These claims have been canceled. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 4-7, 29, 30-32, 67, 70, and 98-100 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims have been canceled. Withdrawal of the rejection is respectfully requested.

Non-Statutory Double Patenting Rejection

Claims 1, 4-23, 25-29, 92-98, and 101-105 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 and 59 co-pending Application No. 09/430,489 (Our Ref. No. 2002850-0003). Applicant submits that the accompanying Terminal Disclaimer removes this ground for rejection and respectfully requests withdrawal of the provisional rejection.

Rejections Under 35, U.S.C. § 102(b)

Claims 1, 4, 5, 14, 15, 22, 23, 25, 26, 28, 29, 92, 98, and 101 stand rejected under 35, U.S.C. § 102(b) as being anticipated by Persson et al. (WO 97/40167). Applicant disagrees.

Claim 1 recites an antibody directed to a conformational epitope of a protein of Hepatitis C virus E2 protein of more than one genotype, wherein the antibody is selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. Claim 92 recites a combination of two or more antibodies directed to two or more different conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype, wherein the antibodies are selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. The remaining claims are dependent on claim 1 or claim 92.

Applicant submits herewith a Declaration under 1.132 and Exhibits A-D demonstrating that the antibodies recited the claims are structurally distinct from the antibodies of Persson et al. and have different antigen binding specificities.

Exhibit A provides some general information about how the antigen binding specificity of antibodies is determined. As explained in the Declaration, the antigen binding portion of an antibody, or the Fab fragment, is made up of a heavy chain and a light chain, each having a variable (V) domain and one or more constant (C) domains. As shown in the top portion of the first page of **Exhibit A**, the light chain contains one variable domain (V_L) and one constant domain (C_L) (see page 1 of **Exhibit A**). The heavy chain contains one variable domain (V_H) and three constant domains (C_H). Each variable domain has three regions that show a high level of amino acid sequence diversity. These "hypervariable regions" (HVRs) are called Complementarity Determining Regions (CDRs) (see page 2, Exhibit A).

Exhibit B is a paper by Xu and Davis, which shows that the diversity in antigen-binding specificity of an antibody is determined mostly by the diversity in sequence of CDR3 of the V_H chain alone. As stated in the Declaration, Xu and Davis created mice constrained to use a single V_H gene (V_H 5-51), but full CDR3 diversity to generate their B cell repertoire. Mice were challenged with a variety of protein and hapten antigens and the development of primary and memory immune responses monitored. (See **Exhibit B**, sections entitled "Experimental System," page 37-38 and "Experimental Procedures," page 43.) As stated in Declaration, Figure 2 shows that these mice respond to antigen challenge with a "normal" immune response (see also page 39, column 1). Xu and Davis also showed that monoclonal antibodies could be generated against a variety of antigens in these mice. When they sequenced the genes encoding the variety of monoclonal antibodies, they found that their sequences differed predominantly in the CDR3

region. Xu and Davis conclude that "the highly diverse CDR3 loops are the key determinant of specificity to antigen recognition."

Persson et al. disclose four Fab molecule clones, 1:5, 1:7, 1:11, and L3. The deduced amino acid sequence of the V_H chain of each antibody is shown in Figures 1A-1D (SEQ ID NOs: 1-4). The deduced amino acid sequence of the V_L chain of each antibody is shown in Figures 2A-2D (SEQ ID NOs: 5-8). The CDR regions (CDR1, CDR2, CDR3) are indicated.

The genes encoding the V_H chain of the antibodies of the present invention were also sequenced, as described in the Declaration and in **Exhibit C**. Specifically, the amino acid sequences of the V_H and V_L genes of CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17 were determined. **Exhibit D** shows alignments of the deduced amino acid sequences of the antibodies of Persson et al. (SEQ ID NOs: 1-4 and 5-8) and the deduced amino acid sequences of the antibodies of the present invention (CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17) (see pages 1-4 and 9-12 of **Exhibit D**). As explained in the Declaration, the alignments show that the sequences of the Persson et al. antibodies are different from the sequences of the antibodies of the invention. Furthermore, there are no identical sequences between any of the CDR regions (CDR1, CDR2, or CDR3) of Persson et al. and any of the antibodies CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, or CBH-17.

Dr. Foung, an expert in the field, reasoned that because the sequence of CDR3 primarily determines the antigen binding specificity of antibodies (Xu and Davis, **Exhibit B**) and because each of the CDR1, CDR2, and CDR3 sequences of our antibodies are different from the CDR1, CDR2, and CDR3 sequences disclosed in the Persson et al. reference, the antigen binding specificities of our antibodies are distinct from the antigen binding specificities of Persson et al.

Thus, the antibodies are structurally distinct from one another and have different binding specificities.

Anticipation under 35 U.S.C. 102 requires that the invention disclosed by the prior art reference must be identical to the claimed invention in each and every aspect. As stated in *Hybritech Inc. v. Monoclonal Antibodies, Inc,* 802 F.2d 1367,231 U.S.P.Q. 81 (Fed. Cir. 1986), "[I]t is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Nowhere do Persson et al. disclose a monoclonal antibody the same as presently claimed. Therefore, the Persson et al. publication cannot anticipate the claimed invention and withdrawal of this rejection under 35 U.S.C. § 102(b) is requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 8-13 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Persson et al. The Examiner states that the antibodies of Persson et al. reasonably appear to be the same or only slightly different from the antibodies of claim 8-13. The Examiner states that the arguments made in the last Response were not found persuasive because they rely on limitations not found in the claims, i.e., the rejected claims do not require hybridomas. The Examiner further states that Persson's antibodies came from an HCV infected donor, and they behave the same way in neutralization assays as Applicants antibodies. The Examiner concludes that the Applicant has provided neither persuasive argument nor factual evidence that Applicant's antibodies as claimed are structurally or functionally different from Persson's.

Claim 8 recites an antibody that binds to a conformational epitope within amino acids 411 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody binds to the E2

protein of Hepatitis C virus of more than one genotype, wherein the antibody is selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitopes as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11. Claim 9 recites an antibody that binds to a conformational epitope within amino acids 470 through 644 of E2 protein of Hepatitis C virus 1b, wherein the antibody is capable of binding to the E2 protein of Hepatitis C virus of more than one genotype, wherein the antibody is CBH-4G, or binds to the same conformational epitopes as CBH-4G. Claim 12 recites an antibody that binds to the epitope recognized by CBH-2, -4D, -4B, -4G, -5, -7, -8C or -11. Claim 13 recites an antibody wherein the antibody competes with CBH-2, -4D, -4B, -4G, -5, -7, -8C, or -11 for binding to its epitope.

Applicant submits herewith a Declaration under 37 C.F.R. §1.132 and **Exhibits A-D** demonstrating that the antibodies recited in claims 1 and 2 are structurally distinct from the antibodies of Persson et al. and have different antigen binding specificities than the antibodies disclosed in the Persson et al. reference. As described above, Persson et al. discloses four antibodies whose heavy and light chain sequences appear in Figures 1A-1D and 2A-2D (SEQ ID NOs: 1-8). The sequences of the Persson et al. antibodies differ substantially from the sequences of the antibodies of the present invention, which are illustrated in Figure 1 of **Exhibit C**. Sequence alignments of the variable regions of the heavy (V_H) and light (V_L) chains of the Persson et al. antibodies and the antibodies of the invention (CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17) are provided in **Exhibit D**.

Comparing the amino acid sequences of Persson et al. to the amino acid sequences of CBH-4B, CBH-4D, CBH-4G, CBH-5, CBH-7, CBH-8C, CBH-8E, CBH-11, CBH-2, and CBH-17, it is clear that none of the sequences are the same. Furthermore, there is a lack of consensus

sequences in the CDR regions, drawing particular attention to CDR3. This is proof that the antibodies of the present claims are not the same as the antibodies disclosed by Persson et al.

The Declaration provided by Dr. Foung and submitted herewith shows that the antibodies of the present invention are not only entirely different in amino acid sequence, but also have different binding specificities as deduced by the differences in the CDR binding regions. As described in the Declaration, **Exhibit B** provides evidence that antibody-binding specificity is determined primarily by the diversity of CDR3 of V_H "alone" (page 40 column 1). **Exhibit B** shows that mice constrained to use a single V_H gene, but full CDR3 diversity, generated a "normal" immune response to different protein and hapten antigens. **Exhibit B** further demonstrates that the mice generated monoclonal antibodies to a variety of antigens. From this data, it was concluded that "the highly diverse CDR3 loops are the key determinant of specificity to antigen recognition" in antibodies. Figure 3 of **Exhibit B** shows a sequence analysis of monoclonal antibodies to different antigens. It is clear that the diversity in sequence of the CDR3 corresponds to the diversity in antigen binding specificity.

Since the Persson et al. antibodies differ so substantially in the amino acid sequence of CDR3, as well as CDR1 and CDR2, from the antibodies of the claims, and because diversity in the CDR3 sequence determines diversity in antigen binding specificity, it can be concluded, as described in Dr. Foung's Declaration, that the antibodies of Persson et al. and the claims differ in antigen binding specificity. As stated in Xu and Davis reference of **Exhibit B**, "diversity at one of these regions, CDR3 of the V_H domain, is sufficient to permit otherwise identical antibody molecules to distinguish between a variety of hapten and protein antigens" (Abstract). Thus, the diversity in the sequences of theCDR1, CDR2, and CDR3 regions of the antibodies of Persson et al. and the present claims is evidence of the diversity in the binding specificity.

In light of the above, withdrawal of this rejection is requested.

Issues raised in the Advisory Action

The Examiner indicated that the previously proposed amendment to claims 1, 8, and 9 might contain an informality in that "epitopes" should be "epitope". Applicant thanks the Examiner for pointing out this inconsistency, and the claims have been amended accordingly to recite "epitope".

The Examiner stated that the proposed amendment to claims 25, 26, and 27 leaves the claim dependent on canceled claim 4. The intent in the Response to Final Office Action was to delete the dependency on claim 4, but the strikethrough was not apparent. Accordingly, the deletion of claim 4 in claims 25, 26, and 27 is now accomplished using double brackets as allowed under newly revised 37 C.F.R. 1.121.

The Examiner pointed out that claim 23 has been amended and should be indicated as such, which is done herein. The Examiner has also suggested that claim 23 as amended raises an issue of new matter since support in the specification was not pointed out. Claim 23 has been canceled.

The Examiner pointed out that claim 92 should be designated as (Currently amended), which has been done herein. The Examiner also asserted that the claim as amended was ungrammatical and potentially indefinite in that the noun "antibodies" does not agree in number with the verb "bind" and the scope of "epitopes" is not clear. Claim 92 has been amended herein to render it grammatically correct and definite. Claim 92 as amended recites "A combination of two or more antibodies, wherein at least two of the antibodies bind to different conformational epitopes of E2 protein of Hepatitis C virus of more than one genotype, wherein each antibody is

selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11, or binds to the same conformational epitope as that bound by an antibody selected from the group consisting of CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11." The claim now makes it clear that at least two different antibodies in the composition bind to different epitopes. Dependent claim 93 has also been amended to render it grammatically more correct.

Conclusion

In light of the foregoing Amendment and Remarks, Applicants respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful or if questions arise regarding the amendment proposed above, please do not hesitate to contact the undersigned at (617) 248-5071.

Please charge any fees that may be required, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

Monica R. Gerber

Monica R. Gerber, M.D., Ph.D.
Registration Number 46,724

Dated: September 17, 2003
PATENT GROUP
CHOATE, HALL & STEWART
Exchange Place
53 State Street
Boston, MA 02109
Tel: (617) 248-5000
Fax: (617) 248-4000